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Preliminary Report on Residual Lung Damage in Long COVID-19 Using AD-cSVF In Clinical Trial NCT# 04326036

Robert W Alexander*
Northwest Institute of Cellular and Biocellular Research USA

***Corresponding author:** Robert W Alexander, Northwest Institute of Cellular and Biocellular Research, USA.

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Introduction

Clinical Trial of Treatment Long COVID-19 Patient Residual Damage

- Overview Summary of Understanding & Management
- Explain Clinical Trial of Use Of cSVF In Long COVID Lung
- Brief Description of cSVF Use In COPD/FLD Patients
- Fluidda Analysis of COVID Lungs (Functional Pulmonary Images) For Diagnosis, Prediction, Management & Outcome Tracking
- Brief Introduction Followed By COVID Background & Beliefs

Understanding COVID-19

- Overview Summary of Understanding & Management
- Explain Clinical Trial Of Use Of cSVF In Long COVID Lung
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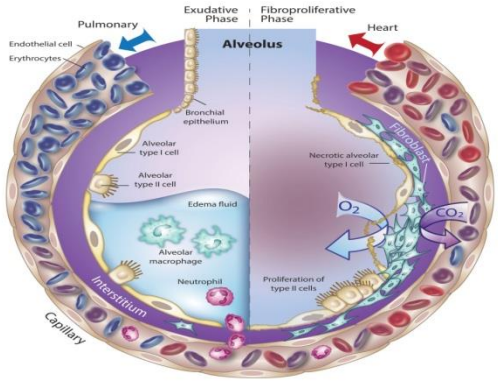
Early Beliefs On COVID-19

- Thought Likely Aerosol and Contact Spread
- Was Uncertain If Man-To-Man Spread (Quickly Dispelled)
- Thought Lungs Were Primary Target Impacted (Is Primary Entry)
- Some Presented ARDS Symptoms (But NOT Respond The Same)
- Presented With Generalized Viral Flu-Like Symptoms/Cough
- High Temps, Dropping 02 Saturations (even on 02), Patient Not Always Aware Sats Falling Below 90
- Mostly Older Patients, Pre-Existing Illnesses, Nursing Homes
- EVOLVED UNDERSTANDING COVID-19
- Immune System Failure, Often Severe Atypical ARDS (ICU, Vent)
- Sudden Loss Lung Respiratory Functional Capacity ***
- Later Stage Huge Immune/Inflammatory Reaction (Cytokine)
- ARDS Progression NOT Following Classic Pulmonary Viral Infections
- Clots-MicroThrombi (Lungs, Heart, Brain, Kidney, Extremities, Liver)
- DIC Noted EVEN In Patients With No Co-Morbidities
- Known Attack Point at ACE2 Cell Wall Receptors (Lungs, Blood Vessel Linings, Kidneys, Intestines, etc.)
- Oxidative Stresses Are Elevated Within COVID-19 Process (ROS)



Alveolus in COVID-19 losing gas exchange capability.

Progressive Alveolar Damage In COVID-19

Image Article | Alexander RW. J Stem Cell Res.*2023, 4(2)-52.*
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Mechanisms Of Lung & Peripheral Clotting In Covid-19

- Damage Occurs In Endothelial Walls Vessels – Many ACE2 Receptors Yielding High Angiotensin II Levels – Same Target as COVID Lung
- Spike Protein Of Virus Targets the ACE2 Receptors (Lungs, Capillary Endothelial Cells & Lung Alveolar Type II Cells, etc.)
- Elevated vWF Levels (Subendothelial) + Factor 8 in Circulation = Clotting
- Increased D-Dimer Levels, Lowered Platelet Levels (Reflects Clotting)
- Patients Display Serious Oxidative Stress & Thrombus Symptoms
- Impaired Gas Diffusion (Vascular Inequality - V/Q Ratio Changes)

Early Management Tried in Covid-19 Ars

- Ventilator Tidal Volumes Were Often Set TOO HIGH
- Often Tried Excessive PEEP Pressures (Both Did Not Raise O2 Sat)
- Tried Supine Vs. Prone Positioning Which Helped (Ref: Guerin – NEJM)
- Failure If Induced Coma Levels Not Enough (Vent Override Issue)
- Caused Over-Distention Lungs + Fluid Leaks into Alveoli (Lower Ventilation/Perfusion Resulted With The "Cytokine Storm" Damage
- Resulted in Infiltration Fibroblasts, Scarring & Alveolar Loss

Common Case Management in Covid-19

- Ventilatory Support Escalation:
- Medium & High Flow O2
- CPAP/BPAP and Select Use Of PEEP
- Intubation & Full Ventilator Monitored TV (Long Term Need Is Common)
- Induced Coma To Permit Ventilatory Support
- Longer Prone Positioning Scheduling (Improves Ventilation)
- Used Steroids, AntiOxidants, AntiCoagulants, Variety of Medications
- NOTE: Often Resulted in Permanent Lung Air Exchange Damage

Clinical Trial Background Using Csvf

- Proposal For Phase 0/I Based On Experiences With cSVF in COPD & Fibrotic Lung Disorders (FLD) in Clinical Trials
- Two Years Of Existing Trials + For Safety and Efficacy In Progress
- FLUIDDA Analytics Available For Functional Respiratory Imaging
- Major Value In Diagnostics, Prognostications, Management
- Study Examines Lung Damage Changes Achieved with cSVF + Other Systemic Findings Common In Long-COVID (>12 Week, Persistent)
- Prognostication Value Permits Early Interventions Needed
- COPD/FLD Group Showing Clinical Improvement In Function

Background & Logic Of cSVF Use

- Studied Homeostasis & Wound Healing
- Examined How We Remodel, Repair & Maintain
- Learning More Stem + Stromal Cells & Their Possible Roles
- Known Importance For Repair/Regen In ALL Tissues
- Site Specific Changes: Microenvironment & Paracrine Functions Appear of Major Importance
- Concentrates Contribute Cells & Signal Proteins (Including Exosomes/MV) To React At Needed Sites
- Has Produced An Excellent Safety Profile In Autologous Use cSVF

Understanding Adult Stem Cells

- Wikipedia: "Adult Stem Cells are multipotent, undifferentiated cells found throughout the body after development, that multiply via Asymmetric Cell Division to replenish dying cells and regenerate damaged tissues".
- Adult stem cells values center on ability to divide & self-renew indefinitely, either generating the SAME cell or other cell types than the tissue from which they originate! (Basis for Multipotency)

Study NCT #04326036

- Harvesting, Isolation/Concentration cSVF (Digestion) – IV Deploy
- FUNCTIONAL RESPIRATORY IMAGING (FRI) – Fluidda Analysis
- Uses HRCT-LUNG (Low Radiation Dose, Thin CT (<1mm), Taken At Functional Full Inhalation/Exhalation) -- Not A Std CT Lung
- Baseline and 6-12 Month Samples For Comparative Analytics
- Baseline and 6 Month Sample Std. PFA For Comparative Analytics
- Monitoring 02 Sats, Supplemental 02 Changes, DOE, etc.

Cellular SVF Use In COPD/FLD

- Known Ability To Mitigate Inflammatory Reactions
- Known Mitigation Immune Responses (Immunomodulatory Effects)
- Autologous, Heterogeneous Cellular, Paracrine, & Signaling Effects
- Elements Includes Innate & Adaptive Immune Response Cell Types
- Non-Designated Cells (MSC, Perivascular Group) + Paracrine Effects
- Known to "Home" To Damaged-Inflamed Areas
- Signaling Via Exosomes/MV Secretions From Key Reparative Cells & Native Local Damaged Area Cells (Cell-To-Cell Communication)

Accessing/Concentrating AD-SVF Components

- Disposable, Sterile Microcannula With Tulip GEMS (2.11 mm)
- Usual Compressed Volume (After Centrifugation) 20-25 cc ATC
- Enzymatic Isolation/Incubation/Concentration Of AD-cSVF (Stem/Stromal Cell Elements)
- Neutralization/Rinsing Of cSVF (Removal Residual Enzyme)

- Resuspension In Normal Saline (Buffered) and Deployment
- Arbitrary Target Minimum Number Of 100 Million SVF Cells To Deploy IV Trial And Verified Flow Cytometry For Numbers, Cell Integrity (Viability Measure), Cell Size Averaging

Disposable Microcannula System

FluiddaAnalytics:

Functional Respiratory Imaging (Fri)

- Been VERY Valuable In Analysis of cSVF in COPD/FLD & COVID-19
- High Resolution CT LUNGS (Functional Exam NOT Chest CT)
- Relatively Low Dose Radiation; Rapid, Thin Section Of Full Inspiration/Expiration
- Proven Value In Diagnostics, Prediction, Tracking Management
- Shows Significant Air Perfusion/Exchange Changes
- Uses CT Lung (at Both TLC and FRC) For Airways & Vascular
- Useful Both In Active & Post-Infection Populations

Example Covid-19 Hrct Images

Covid-19 Moderate Damage

Covid-19 Severe Damage (Scarring)

Image Article | Alexander RW. J Stem Cell Res.*2023, 4(2)-52.*
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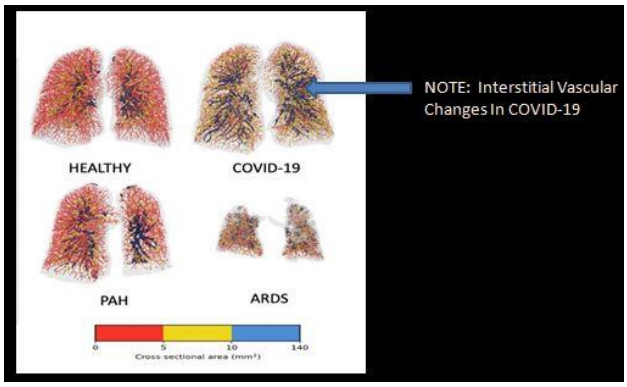
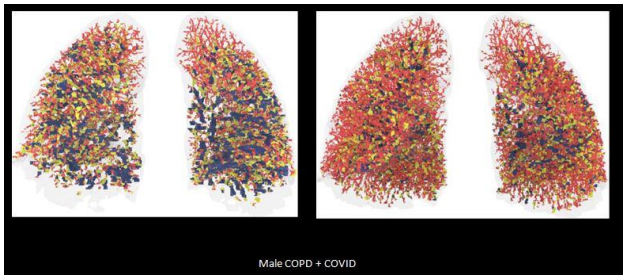
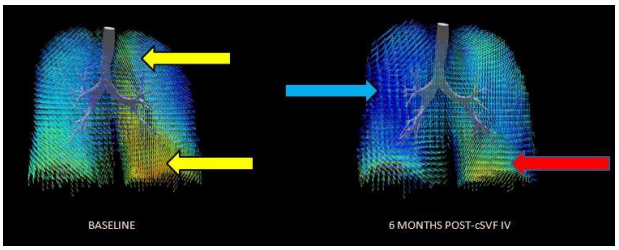
Vascular Patterns in Lung Diseases



Trial Patient #7: Vascular Changes



Ventilation/Perfusion Changes With cSVF



Example: Actual Exam Baseline-6 Months

Trial Patient #8 – Perfusion Impact

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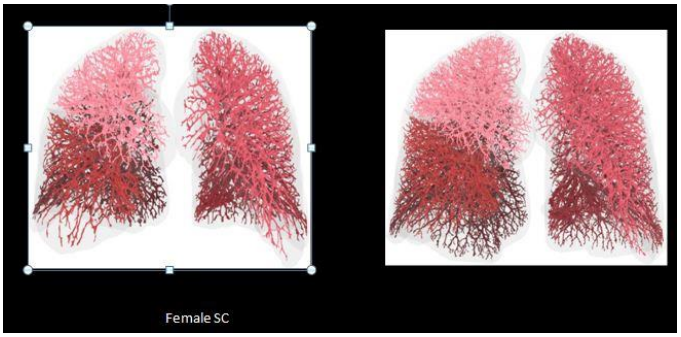
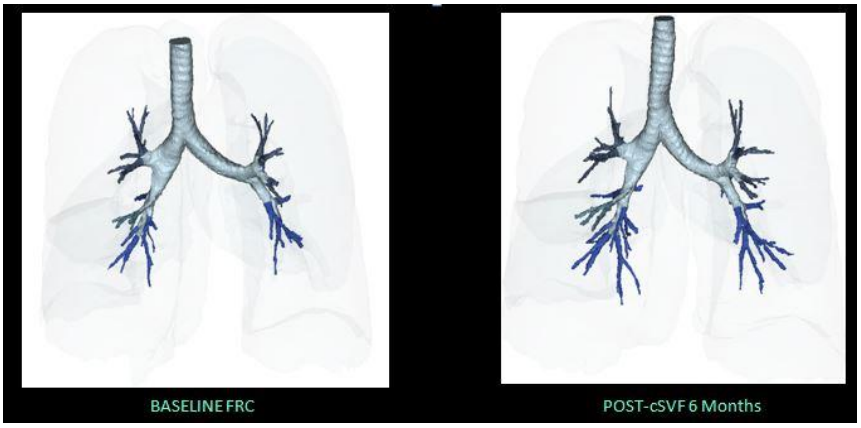
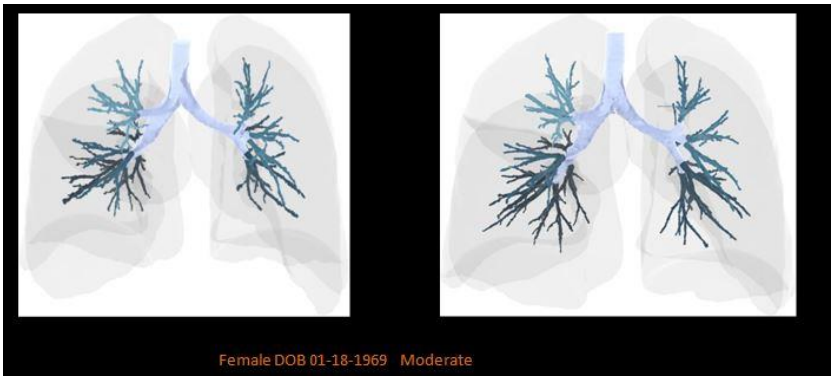


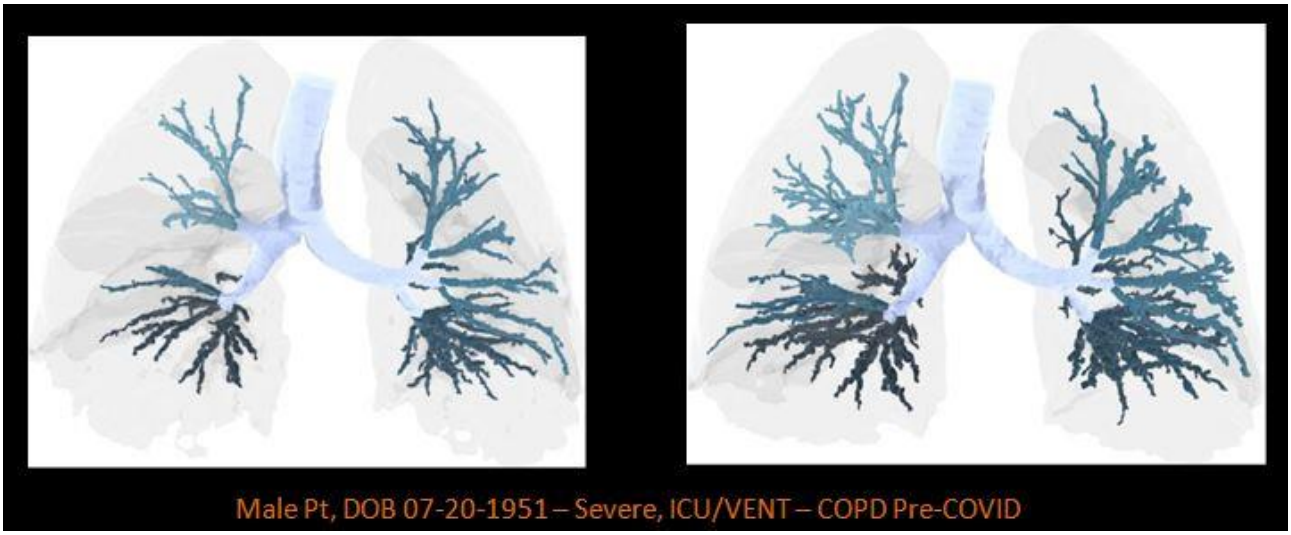
Fluidda Analysis: Frc (Actual Copd Patient)



Trial Patient #8: Fluidda Analysis



Trial Patient #1: Fluidda Analysis



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